

# MIS-C is a Clinically Different Entity from Acute COVID-19 in Adults

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We appreciate the authors for their interest in our case report and are thankful for their critical appraisal. They have expressed their reservations about some statements made in the text, but it seems they have missed the actual timeline, sequence of events, and the already-embedded information in the original text.<sup>1</sup> We have tried to clarify all the concerns raised, with special reference to the timeline of events.

At the outset, we would like to emphasize that the index case is about "multisystem inflammatory syndrome in children (MIS-C)," which is a clinical entity different from "acute COVID-19" as seen and described in adults. MIS-C usually represents a postinfectious, immune-mediated complication, occurring 2 to 6 weeks after primary exposure (as happened in our case), rather than an acute infection.<sup>2</sup> The knowledge and understanding of MIS-C is gradually evolving over the last 1 year. The main purpose of our case report was to highlight the "severe" neurological insult involving "both central and peripheral nervous system" as a spectrum of MIS-C, which has been rarely reported in the literature available till date.

- Central and peripheral neurological insult in our case manifested at different time intervals, though the onset of illness probably happened simultaneously. The first neurological insult was suspected on the 7th day of hospitalization when the child on ventilatory support did not show improvement in sensorium, despite being off sedatives for 48 hours. Neurological assessment at this juncture (in an intubated child) done by the Glasgow Coma Scale showed the complete absence of motor and eye response to painful stimuli (M-1, E-1). Pupillary reflexes were normal. The next day she developed repeated generalized convulsions. MRI brain with contrast was done as an emergency procedure (with child on midazolam infusion for seizures). MRI spine was not done at this time as no spinal involvement was suspected, and it was technically difficult too. Lumbar puncture was deferred in view of presence of cerebral edema reported in neuroimaging and critically sick condition of the child. Based on clinical history and neuroimaging findings, acute disseminated encephalomyelitis (ADEM) was kept as the most plausible diagnosis and accordingly managed. Second neurological insult manifested in the 3rd week of illness when the child (still on ventilatory support, tracheostomized) showed improvement in sensorium for the first time since admission, but her first formal assessment of muscle power revealed quadriplegia in all limbs (power 1/5) with bifacial and diaphragm involvement (assessed by bedside ultrasound). Deep tendon reflexes were absent in all limbs. Sensation to touch and pain was intact. Nerve conduction study (NCS) findings showed symmetrical

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axonal motor polyneuropathy involving limbs and diaphragm, without sensory nerve involvement (already mentioned in case report). Possibilities of both "critical illness-related neuropathy" and "Guillain-Barre Syndrome (GBS)" were kept; however, the treating team considered the diagnosis of GBS in view of the absence of sensory nerve involvement and the presence of bilateral facial and phrenic nerve involvement. Lumbar puncture at this juncture was again deferred because the onset of GBS had probably started earlier at the admission, and in the 3rd week, cerebrospinal fluid (CSF) analysis would not have benefitted the patient, as IV-Ig, steroids, and plasma exchange had already been given. Still, in the manuscript, we have refrained from the repeated use of "ADEM" and "GBS", as clear-cut diagnosis was always skeptical. However, we strongly feel that the clinical presentation, progression of the overall disease and its improvement with immunomodulation, is consistent with acute demyelinating event. We agree with the authors that CSF analysis is important in the evaluation of ADEM and GBS; however, these are still supportive investigations, and their diagnosis in critically sick children is essentially clinical, with supportive evidence from radiological and electrophysiological studies, respectively.<sup>3,4</sup> Even with respect to Brighton Collaboration criteria for GBS, to reach level 2 either CSF or NCS is required.<sup>5</sup>

- None of the neurotoxic drugs that the authors have sought were administered before or during the course of hospitalization.
- We do not agree with the notion that central and peripheral nervous system involvement are the common occurrences of MIS-C; however, it may be partially true for acute

**Table 1:** Reference values of laboratory parameters

	Normal range		Normal range
Hemoglobin (gm/dL)	12–15	C-reactive protein (mg/dL)	0–0.5
Total leukocyte count ( $\times 10^9$ cells/L)	4.0–10.0	IL-6 (pg/mL)	0–7
Platelet ( $\times 10^9$ cells/L)	150–410	Ferritin (ng/mL)	11–306
S. urea (mg/dL)	15–38	D-dimer (ng/mL)	0–243
S. creatinine (mg/dL)	0.26–0.77	Fibrinogen (mg/dL)	238–498
SGOT (IU/L)	<50	Triglycerides (mg/dL)	<150
SGPT (IU/L)	<50	Troponin-I (ng/mL)	0–0.04
Total bilirubin (mg/dL)	0.3–1.2	NT-proBNP (pg/mL)	0–450
Direct bilirubin (mg/dL)	0.1–0.5	LDH (U/L)	98–192
S. albumin (gm/dL)	3.5–5.0		

COVID-19-related symptoms as seen in adults. Myalgia, dysgeusia, and anosmia are symptoms described during “acute COVID-19” illness. As described above, comparing symptomatology of two different clinical entities (acute COVID-19 in adults and MIS-C) is totally irrational.<sup>2</sup>

- Infliximab was not considered in the management of this case, as multiorgan dysfunction (shock, renal failure, and acute respiratory distress syndrome (ARDS) had improved by day 7 with IV-Ig and steroids only.
- Electroencephalogram (EEG) done, while on ventilator, was suggestive of diffuse cerebral dysfunction.
- Again, as the case report refers to post-COVID-19 MIS-C and not acute COVID-19 with cardiac dysfunction, shock observed in MIS-C is vasodilatory, cardiogenic, or a combination of both.<sup>6</sup> Left ventricular dysfunction seen in MIS-C is mostly due to acute myocarditis. In our case, clinical presentation was consistent with a combination of vasodilatory and cardiogenic shock, which probably occurred secondary to cytokine storm (low ejection fraction, elevated NT-proBNP and trop-I, and high inflammatory markers). Improvement after IV-Ig and steroids further supports the diagnosis of acute myocarditis. Initial echo was done when the child had already been put on inotropic support, and this could explain the mild left ventricle (LV) dysfunction at the time of examination. There was neither intraventricular thrombus nor any feature suggestive of takotsubo cardiomyopathy. Elevated NT-proBNP signifies acute myocardial wall stress, and its direct correlation with ejection fraction is still an area of debate, especially in pediatrics.<sup>7</sup>
- The various clinical manifestations in the index case consistent with MIS-C are already mentioned in the case report (generalized erythroderma, persistent vomits and loose stools, shock, elevated cardiac enzymes, LV dysfunction, and elevated liver enzymes).
- Reference values of important laboratory parameters are given in Table 1.

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